Radiothérapie par minifaisceaux

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In the last decades

- 2D radiotherapy
- 3D conformal radiotherapy
- Intensity modulated RT
Radiotherapy: modeling biological response

- **Temporal fractionation**
- **Spatial fractionation**
- **Standard RT**

- LINACS $\rightarrow$ MV photons/e- (95%)-protons-hadrons (5%)
- 2 Gy/session, 1 session per day, 5 days/week
- Dose rate $\sim$ 2 Gy/min
- Field sizes $>$ cm$^2$
- Homogeneous dose distributions
Radiotherapy: modeling biological response

Physical dose → Biological dose

Physical parameters of irradiation
- Type of radiation
- Beam energy
- Delivery mode: dose rate, spatial and temporal distributions, etc.

Biological effect of the radiation
- Tumor control probability
- Normal tissue complication probability

Biological factors
- Tumor type
- Tumor microenvironment
- Genetics
Spatial fractionation of the dose

Conventional RT

Spatially fractionated RT

\[ PVDR = \frac{D_{\text{peak}}}{D_{\text{valley}}} \]
RT techniques based on a spatial fractionation of the dose

GRID Therapy (few hospitals in the world)

1909 Alban Kohler used a “perforated screen” (grid) → effect similar to treatment with small pencil beams.

Widely used in the 1950s as a way to reach tumors deep in the body with kilovoltage beams.

From the 70s GRID therapy with megavoltage radiation beams → palliation of selected, massive and bulky tumors

Improved response to RT and may possibly have cell killing effects outside the directly irradiated area

Beam sizes > 1 cm$^2$

PVDR from 2 to 5
Radiotherapy: modeling biological response

- Physical dose
  - Type of radiation
  - Beam energy
  - Delivery mode: dose rate, spatial and temporal distributions, field size, etc.

- Biological dose
  - Tumor control probability
  - Normal tissue complication probability

Biological effect of the radiation

- Physical parameters of irradiation
- Biological factors
  - Tumor type
  - Tumor microenvironment
  - Genetics
Dose-volume effect: the smaller the field size is, the higher the tolerance

Zeman et al., Science (1959)
More recent examples with high energy photons

The stem-cell depletion hypothesis → for each organ exits a limiting critical volume, which can be repopulated by a single surviving stem cell and for which damage can be repaired by repopulation (Yaes & Kalend, 1988; Yaes et al, 1988).

Novel RT techniques based on “different” delivery modes

Combination

very small field sizes (< 1mm²) + Spatial fractionation of the dose

Dose-volume effects

Zeman et al., Science (1959)

Conventional RT
Novel RT techniques based on “different” dose delivery methods

Dose-volume effects $\rightarrow$ exponential increase of healthy tissue tolerances

+ 

Spatial fractionation $\rightarrow$ gain in healthy tissue recovery $\rightarrow$ increase of healthy tissue tolerances
Novel RT techniques based on “different” dose delivery methods

Dose-volume effects $\rightarrow$ exponential increase of healthy tissue tolerances

+ 

Spatial fractionation $\rightarrow$ gain in healthy tissue recovery $\rightarrow$ increase of healthy tissue tolerances
Synchrotron micro and minibeam radiation therapy

- Submillimetric field sizes (25 to 700 µm)
- Interbeam separation (400 to 3500 µm)
- Dose profiles consist of a pattern of peaks and valleys
- Kilovoltage beams
Minibeam Radiation therapy

High resistance of normal tissues

Doses as high as 100 Gy/session are still well-tolerated by the rat brain in comparison to 22 Gy in RT conventional

Prezado et al, Rad. Research 2015

A factor 3 increase in lifespan of glioma bearing rats

Biological effects not well understood

• Cell migration seems to be the responsible for tissue reparaison

• Differential effect normal-tumoral tissues

  o *Induction of denudation of tumor vessel endothelium, of a decrease in tumor blood volume as well as of tumor hypoxia.*

  o *The bystander effect/cellular communication.*

  o *A significant transcriptomic modulation for 30 genes in intracranial tumor tissue following spatial fractionation techniques, undetected in normal tissue \(\rightarrow\) mainly related to the regulation of cell cycle and to immune/inflammatory response.*
x-rays MBRT: possible transfer from synchrotrons to cost-effective equipment

IMNC + Campus d'Orsay + INSERM U836
Radiobiology platform (Institut Curie)

Synchrotron → low cost equipment

- Feasibility evaluation: modification of the irradiator (patent)
- Biological studies → understand the involved mechanisms (starting Autumn)
Radiotherapy: modeling biological response

Physical dose $\rightarrow$ Biological dose

Physical parameters of irradiation

Type of radiation
Beam energy
Delivery mode: dose rate, spatial and temporal distributions, field size, etc.

Tumor control probability
Normal tissue complication probability

Biological effect of the radiation

Tumor type
Tumor microenvironment
Genetics

Biological factors
In a recent work: Monte Carlo proof of concept suggested a possible way to generate minibeams of protons and highlighted advantages of this approach [Prezado 2013]:

- Spatial fractionation in healthy tissue
- Homogeneous distribution at the Bragg peak location
Implementation at the Proton Therapy Center Orsay

- **Spatial fractionation** of the dose in the normal tissue beyond the Bragg peak

- **Quasi-homogeneous** dose distribution at the Bragg peak location due to multiple Coulomb scattering in depth
Potential renewed use of very heavy ions for therapy

- Very heavy ions (Ne or heavier) used in the past, very effective for the treatment of hypoxic/resistant tumors (Castro 1994)
- However abandoned due to important side effects in normal tissues

**Combination**: MBRT + heavy ions therapy

- → **MBRT**: increase healthy tissue sparing
- → **Heavy ions**: increase tumour cells killing capacity

Very heavy electrons for therapy

E ~300 MeV  At  hospitals E ~ 2 – 25 MeV

Potential clinical advantages that can be investigated:

-Lateral electromagnetic scanning could have certain clinical advantages that are not possible by using photon beams. This can be advantageous for image-guided energy- and intensity modulated radiation therapy

- a possible gain in relative biological effectiveness (RBE) might be observed.
High energy electron grid therapy: collaboration with LAL

View of the grid

2D dose distributions

For a human head 250-300 MeV are required

Martinez & Prezado, Med. Phys. 2015

Technical implementation—collaboration with LAL
Conclusions

• We are still far away from having found the optimum way to use ionizing radiation for therapy

• Some relevant radiobiological effects/mechanisms only recently explored

• Physics parameters of the irradiation can be used to model the biological response – to improve treatment outcome

• Advancements in radiotherapy require a interdisciplinary approach
Thank you for your attention

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